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Role of Clinical and Genealogical Analysis of Genealogical Trees in the Gynaecologist's Practice

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Abstract.

The results of medical-genetic counselling introduction are presented in the article basing on the results of the questionnaire survey of 750 females during general gynaecological admission in order to reveal the families with tumour pathology aggregation. The analysis of clinical-genealogical data of the females from such families determined that malignant tumours association in their families corresponded to familial cancer syndrome (Lynch syndrome II) or hereditary cancer. Basing on the results of complex clinical examination of 73 probands who had malignant tumours aggregation in their genealogical trees, malignant and premalignant processes in female reproductive system organs were detected. The obtained data indicated the effectiveness and reasonability of questionnaires as a simple screening method during gynaecological admission to reveal the families with tumour pathology accumulation and to plan further extended individual examination for females from such families aiming on timely detection and treatment of benign pathology of female reproductive system organs and cancer development prevention.

Problem statement and analysis of the recent research

Malignancies prevention and early diagnostics are the most important social-medical problems in oncology. This thesis relates entirely to cancer of female reproductive system organs (FRSO), the morbidity rate of which does not tend to decrease in Ukraine according to the data of the National Cancer Register of the Institute of Cancer of Ukraine. In the structure of female oncologic pathology cancer of breast, uterus, and ovaries occupy the first rank places. [1-4].

Clinical studies demonstrate that despite significant progress in improving of methods for oncologic patients' treatment and application of new cytostatic agents their mortality rate does not tend significantly to reduce due to diagnostics of tumor processes at the late stages of their development. Therefore, from the position of anticancer strategies, the priority is given both to prevention, and to early diagnostics of precancer and cancer; however these problems solving is complicated by the lack of organized systems and scientifically based programs. At the same time, one of the effective measures facilitating early diagnostics of precancer and cancer is the development of screening programs. The aim of such programs is to detect the disease at early stages of its development, when the symptoms are still absent and curative treatment is possible. One can differentiate between universal and selective screenings; the latter is performed in risk groups concerning the occurrence of specific disease [6-8]. In our opinion, the achievements of clinical oncogenetics, where theoretical basics of genetics and molecular biology of tumor growth, and also practical experience of oncologists regarding hereditary and family cancer forms of the cancer of breast, ovaries, uterus, colon and other tumors are integrated, may be included into selective risk programs [3-5].

The objective of the research was to determine the role of clinical-genealogical analysis of genealogical trees for determination of families with familial cancer syndrome, and as a stage of genetic screening of the initial forms of cancer of female reproductive system organs.

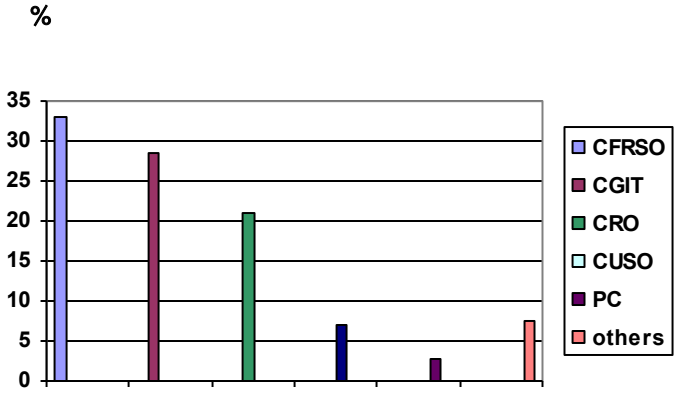
Material and methods of the research involved seven hundred and sixty clinical-genealogical questionnaires, results of clinical-genealogical and clinical-morphological examination of 73 females from families with familial cancer syndrome.

Results of the research

Seven hundred and sixty females, who visited gynecologist for prophylactic examination, completed questionnaires for medical-genetic counseling by themselves. According to the questionnaires data in the families of 73 females (9.6%) the cancer patients were indicated comprising 172 persons in total. Association of different genesis tumors in families became the reason for familial cancer syndrome (FCS) diagnostics. Total number of tumors in 73 genealogical trees was 182, among them there were tumors of FRSO, cancer of gastro-intestinal tract (GIT), cancer of respiratory organs, urinary system, prostate and others. Association of different genesis tumors (cancer of FRSO, GIT, respiratory organs and urinary system, prostate, Hodgkin's disease and others) suggested the occurrence of familial cancer syndrome (FCS) in the families. As it may be seen from the Table 1, the majority of tumors (60/33%) were FRSO cancers. Their numeric distribution demonstrated that breast cancer and uterine cancer prevailed (46.7% and 30.0%, respectively), ovarian cancer (OC) was less frequent (20.0%), and uterine cancer comprised only 3.3%.

All the females that sought counseling underwent complete examination which included gynecologist's examination, ultrasound examination of small pelvis organs and abdominal cavity, mammary and thyroid glands, mammography, fibrogastroscopy, colonoscopy, blood and urine analyses. This provided an opportunity to diagnose pathological processes of benign (49/67.1%) and malignant (24/32.9%) nature in 73 (9.6%) of females who had relatives with cancer in their genealogical trees. Their numeric distribution with detected pathology of benign nature depending

on clinical diagnosis and age is presented in Table 1, according to which the most frequently detected pathological processes were the ones in uterine corpus (23/31.9%) – uterine myoma, adenomyosis, atypical hyperplasia of endometrium, less presented were the processes in uterine cervix (19/26.4%) - CIN2-3, endocervicosis, and chronic endocervicitis. The rate of females with ovarian and uterine tubes pathology (polycystosis and ovarian cysts) and mammary gland (fibroadenomatosis and cysts) was similar –14 (by 19.4%) observations each; in 2 females (2.8%) thyroid gland pathology was diagnosed.



Types of malignant tumors in the family trees

Figure 1. Numeric distribution of tumors (%) in 760 genealogical trees.

Note. CFRSO – cancer of female reproductive system organs; CGIT – cancer of gastro-intestinal tract; CRO- cancer of respiratory organs; CUSO – cancer of urinary system organs; PC – prostate cancer.

Table 1

Numeric distribution of malignant FRSO tumors (%) depending on their localization (according to clinical-genealogical data of 60 family trees)

Localization of tumors	Number of tumors	
	n	%
Breast cancer	28	46.7
Uterine corpus cancer	18	30.0
Ovarian cancer	12	20.0
Cervical cancer	2	3.3
Total	60	100.0

Table 2

Numeric distribution of females with detected pathology of benign nature depending on clinical diagnosis and age (n=49)

Benign processes	Number of patients n (%)	Patients' age
Uterine myoma	14 (28.6)	23-57
CIN2-3	13 (26.5)	27-65
Fibroadenomatosis of mammary	12 (24.5)	25-43
gland	10 (20.4)	23-68
Ovarian polycystosis	8 (16.3)	28-55
Uterine adenomyosis	5 (10.2)	23-32
Endocervicosis	3 (6.1)	27-50
Ovarian cyst	2 (4.1)	17, 57

Mammary gland cyst Thyroid gland hyperplasia Atypical endometrial hyperplasia Hydrosalpinx Chronic endocervicitis	2 (4.1) 1 (2.0) 1 (2.0) 1 (2.0)	29, 43 43 49 32
Total	**72 / 100%**	17 – 68 (mean age 48±4.3 years)

Numeric distribution of patients with detected malignant pathology depending on clinical diagnosis and age (n=24) is presented in Table 3, where it can be seen that the most frequent diagnosed malignant processes were those in FRSO (18/75%). In the genealogical trees according to the data of clinical-genealogical analysis 33 relatives were detected suffering from cancer of FRSO, GIT and other malignant tumors; moreover, after genealogical trees analysis it was proved that the majority of relatives with cancer were on the maternal side (27/81.8%). Due to timely diagnostics during probands examination after medical-genetic counseling in the majority of cancer patients the tumors were detected at the stage I (14/58.4%).

Table 3

Numeric distribution of patients with malignant pathology depending on clinical diagnosis and age (n=24)

Diagnosis	**Stage**	**Age**	**Cancer burden of genealogical tree**	**Treatment methods and survival**
Cervical cancer (7=29.1%)	0-1A1, 3A	31-39	In 4 patients two cases of uterine corpus cancer (UCC) each in the family (mothers and grandmothers on the maternal side) and in 2 patients 1 case of UCC for each in the family (mother) = altogether **10 relatives** suffering from cancer in the genealogical trees.	All patients received organ-saving surgical treatment: cervical conization and/or amputation, follow-up and relapse-free period for 3-6 years.
Breast cancer (6=25.0%)	1A-2B	43-51	In 4 patients BC was in grandmother on the maternal side, in another 2 patients – in mother = altogether **6 relatives** suffering from cancer in the genealogical trees.	Relapse-free follow-up period for 3-5 years after complex treatment completion (surgery + radiation therapy+6 PCT courses with the scheme "CC".
Ovarian cancer (3=12.5%)	1C	36-51	In I patient UCC in mother and OC in grandmothers on the maternal side, in 2	Relapse-free follow-up period for 5-7 years after complex treatment (surgical panhisterectomy and

			patients mother suffered = altogether **4 relatives** suffering from cancer in the genealogical trees.	omenectomy + 6 PCT courses with the scheme "CC".
Uterine corpus cancer (1=4.2%)	1	55	CC in father and mother = altogether **2 relatives** suffering from cancer in the genealogical trees.	Relapse-free follow-up period for 6 years.
Uterine sarcoma (1=4.2%)	1	64	Altogether **1 relative** suffering from cancer in the genealogical tree (CC in the grandmother on the maternal side).	Relapse-free follow-up period for 5 years.
Thyroid cancer (1=4.2%)	1	47	Altogether **2 relatives** suffering from cancer in the genealogical trees (lung cancer in father and grandfather on the paternal side).	Relapse-free follow-up period for 5 years. .
Colon cancer (4=16.7%)	2	54-72	Altogether **5 relatives** suffering from cancer in the genealogical trees (2 cases of CC in 1 patient = mother and father suffered from cancer, in 3 patients = 1 case of gastric cancer or CC each, grandfather and grandmother on the maternal side suffered from cancer).	Relapse-free follow-up period for 7-9 years
Hodgkin's disease (1=4.2%)	3B	49	Altogether **3 relatives** suffering from cancer in the genealogical trees (leucosis in sister, father and grandfather on the paternal side suffered from lung cancer).	Lived for 7 years
Total	24	31 – 72 (mean age 57.5±2.2 years)	Altogether **33 relatives** suffering from cancer in the genealogical trees (from them 27 relatives with cancer were on the **maternal side – 81.8%)**	All the patients are under observation – relapse-free period is from 3 to 9 years.

All the females with detected oncologic and precancer pathology received treatment according to the standards established in Ukraine. These females together with their relatives were assigned to the groups of potential genetic risk of oncologic pathology development, considering the possibility of primary-multiple malignant tumors development in the families with FCS. In addition, the individual plan of dispensary observation was made for each female with fixed dates of repeated visits and examinations.

Hense, from the list of benign processes the significant number of pathological processes, which may cause hormonal homeostasis disorders is noteworthy. These disorders have complex pathogenesis, as the disorder of cyclic processes of hypothalamo-hypophysial-ovarian systems is known to lead to alteration of sexual hormones reception and, in general, to hormonal balance alterations [1-5]. Such changes in hormonal reception are the cause of ovulatory and menstrual functions deteriorations that promote the development of such conditions as endometriosis, uterine myoma, hyperplastic processes in endometrium, ovarian cysts and polycystosis, and mammary gland fibroadenomatosis. Fundamental studies demonstrated two major mechanisms of hormone action: promotor (physiological), that is hormone action is directed at cells division stimulation, and genotoxic, when the hormones or their derivatives affect DNA structure inducing mutations that cause genome instability, and may facilitate tumor grown initiation and promotion [2, 6-8]. From the standpoint of the presented above information, the significance of hormonal homeostasis disorder, morphological equivalents of which are changes in the described patients with FCS in their families, has extremely important clinical significance. This is a reasonable basis to include such patients into genetic risk groups of cancer development because it was demonstrated that in FCS cases germinal mutations in the genes – suppressors of tumor growth *BRCA1* and *BRCA2* [3-5] are seen. The transfer of these mutations from generation to generation according to laws of heredity and presence of hormonal homeostasis disorders are the risk factors of tumor development in such situations. All this is a valuable proof of the fact that the knowledge of family and individual cancer history and testing of mutations in the genes – suppressors should become supplementary criteria in the strategy of genetic prophylaxis and screening of FRSO cancer. The obtained results demonstrate the reasonability of application and introduction of medical-genetic counseling of females from the families with tumor pathology aggregation. The obtained results may form a basis for establishment of the register for families with familial cancer syndrome and hereditary cancer in female population of Cherkassy region.

Conclusions

1. Among the genealogical trees of 760 females 73 (9.6%) families were detected having tumor aggregation by FCS type. At clinical-genealogical analysis of genealogical trees with FCS were determined in 67.1 % of females with benign processes and in 32.9% of women with malignant processes of different genesis. **FRSO cancer rate was 82.2%. In 14 (58.4%) of 24 patients the malignant process was diagnosed at stage I**.
2. Clinical and genealogical analysis of the families and the knowledge of family and individual cancer history is an effective approach to reveal the families with FCS, and complex clinical-morphological examination of such persons allows detecting benign processes, including precancer processes and tumor processes at initial stages.
3. Knowledge of family and individual cancer history, along with testing of mutations of genes-suppressors of tumor growth *BRCA1* and *BRCA2*, allows detecting genetically determined forms of FRSO cancer, which is a basis for organization of genetic screening in the system of preventive measures and diagnostics of early forms of tumor processes.

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